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Ectrodactyly-Ectodermal Dysplasia-Clefting Syndrome and Hypothalamo-Pituitary Insufficiency

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We report on 2 brothers with ectrodactyly-ectodermal dysplasia-clefting (EEC) syndrome and hypothalamo-pituitary insufficiency. Both had hypogonadotropic hypogonadism. One brother had partial TSH and prolactin deficiency, and the other had mild primary hypothyroidism, due most probably to irradiation therapy which he had undergone a few years earlier because of Hodgkin disease. The association of hypogonadotropic hypogonadism with EEC was reported once previously. Hypothalamopituitary dysfunction could be considered as yet another manifestation of EEC syndrome. This report reconfirms that EEC syndrome is a pleiotropic trait with reduced penetrance. Alternatively, we may be dealing with a (new) autosomal or X-linked recessive condition. Am. J. Med. Genet. 68:168–172, 1997
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KEY WORDS: EEC syndrome; hypogonadotropic hypogonadism; autosomal dominant

INTRODUCTION

Ectrodactyly-ectodermal dysplasia-clefting (EEC) syndrome (ectrodactyly or lobster-claw deformity, ectodermal dysplasia, and cleft lip and palate) is a complex, pleiotropic, rare, autosomal-dominant syndrome [Brill et al., 1972; Rüdiger et al., 1970]. The most common clinical manifestations are ectodermal dysplasia (anomalies of hair, teeth, nails, nasolacrimal ducts, and sweat glands), ectrodactyly (split hand and foot anomalies), cleft lip/palate, and genitourinary anomalies. Other clinical manifestations include deafness and mental retardation [Küster et al., 1985; Preus and Fraser, 1973; Rodini and Richieri-Costa, 1990; Rollnick and Hoo, 1988; Rüdiger et al., 1970]. There is wide variability of clinical expression, and occasional nonpenetrance [Annerén et al., 1991; Majewski and Küster, 1988; Penchaszadeh and de Negrotti, 1976; Predine-Hug et al., 1984; Preus and Fraser, 1973; Schmidt and Nitowsky, 1977; Rodini and Richieri-Costa, 1990; Tse et al., 1990; Walker and Clodius, 1963]. No symptom seems to be obligatory [Küster et al., 1985].

Van Maldergem et al. [1992] previously reported on a boy with EEC syndrome and hypogonadotropic hypogonadism. Knudtzon and Aarskog [1987] described 2 patients with EEC and isolated growth-hormone deficiency. We report on 2 brothers with EEC syndrome and hypothalamopituitary deficiency, manifested mainly by hypogonadotropic hypogonadism. Considering our cases and the previously reported cases, we suggest that hypothalamopituitary insufficiency be accepted as yet another manifestation of EEC syndrome. Since our patients were born to young, nonconsanguineous, and unaffected parents, we confirm that EEC syndrome is a variable, pleiotropic trait with reduced penetrance.

CLINICAL REPORTS

Patient 1

B.Z., a 21-year-old man, was born as the second child to young, healthy, and nonconsanguineous parents of Jewish Sephardic origin. Pregnancy and delivery were normal. Birth weight (BW) was 3,400 g. Initial examination showed a cleft lip, which was repaired at age 3 months.

At age 15 years he was evaluated by an endocrinologist because of delayed puberty, and he was treated with testosterone for 2 years. At age 21 years he was examined by our geneticist, who concurred with the diagnosis of EEC syndrome.

On physical examination a repaired cleft lip, synophris, and flat maxillae were noted (Fig. 1a). Dental examination showed hypodontia, microdontia, and peg-shaped teeth. Height was 179 cm (75th centile), and

Abbreviations: TSH, thyroid stimulating hormone; ACTH, adrenocorticotropin hormone; LHRH, luteinizing hormone releasing hormone; LH, luteinizing hormone; FSH, Follicle stimulating hormone; TRH, thyrotropin releasing hormone.

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Fig. 1. Facial appearance (**a**) and feet (**b**) of patient 1.

weight was 70.4 kg (79th centile). He lacked the right fourth toe (Fig. 1b). He was at pubarche Tanner stage 4, genitalia stage 3; the testes measured 3 ml. Psychomotor development and the rest of the physical findings were normal.

ACTH stimulation test showed normal adrenal response. Growth hormone levels after arginine stimulation reached a peak level of 6.8 µg/l (normal, >10 µg/l). Plasma testosterone level was low (<0.7 mmol/l), as were basal levels of LH and FSH (LH, 0.7 IU/l; FSH, 1 IU/l) and their response to 25 µg/m^2 of LHRH iv. (LH, 0.7–5.4 IU/l; FSH, 1–2.8 IU/l). Prolactin level was 53 mU/l. Levels of TSH and prolactin after TRH stimulation reached low peak levels of 6.9 mU/l and 382 mU/l, respectively, indicating partial pituitary insufficiency. Chromosomes of peripheral blood lymphocytes were normal (46;XY). Magnetic resonance imaging showed a very small pituitary gland (Fig. 2).

Patient 2

B.A., the 16-year-old younger brother of patient 1, was born following a normal pregnancy and delivery. BW was 3,300 g. He had cleft lip and palate (which was repaired at age 2 months), syndactyly of the left third and fourth fingers, and polysyndactyly of the left foot. At age 6 years he developed Hodgkin disease and was treated with chemotherapy and "mantle" irradiation. At age 12 years he underwent corrective surgery for syndactyly of the left hand. At age 11 years he was evaluated by our endocrinologist following radiation therapy. His height was 136.5 cm (35th centile), and weight was 27 kg (10th centile). The penis was small (3 cm long), as were the testes (1 ml). At age 13 years, serum testosterone level was low (<0.2 mmol/l), as were levels

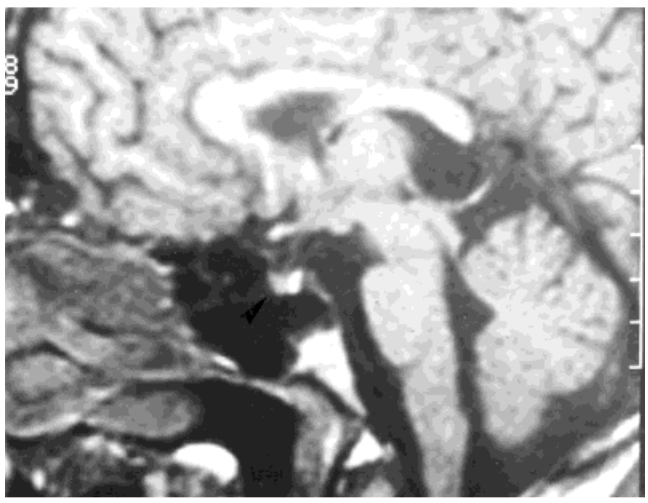

Fig. 2. MRI of brain of patient 1, showing a hypoplastic pituitary gland.

Fig. 3. Facial appearance (**a**), teeth (**b**), feet (**c**), and left hand (**d**) of patient 2.

of LH and FSH (LH, <0.5 IU/l; FSH, 0.7 IU/l). Thyroid function tests showed hypothyroidism.

At age 16 years he was referred to our genetic clinic. Examination showed a repaired cleft lip and cleft palate, flaring eyebrows, flat maxillae (Fig. 3a), hypodontia, microdontia, and peg-shaped teeth (Fig. 3b). Height was 155 cm (<3rd centile), and weight was 44 kg (3rd centile). He had polysyndactyly of the left foot (Fig. 3c), and the left hand showed scars following surgical separation of the third and fourth fingers (Fig. 3d). Pubarche was at Tanner stage 4 and genitalia at stage 3, and the testes measured 3 ml. Psychomotor development and the rest of the physical findings were normal.

ACTH stimulation test showed normal adrenal response. Growth hormone after arginine stimulation reached a peak level of 21.7 μg/l (normal, >10 μg/l). Plasma testosterone level was low (<0.7 mmol/l), as were basal levels of LH and FSH (LH, <0.5 IU/l; FSH, 0.6 IU/l), and their response to 25 $\mu g/m^2$ of LHRH iv (LH, 2.8 IU/l; FSH, 4.6 IU/l). Prolactin level was 163 mU/l. TRH stimulation tests showed an exaggerated response of both TSH (48.4 mU/l) and prolactin (535 mU/l), consistent with mild primary hypothyroidism.

Chromosomes of peripheral blood lymphocytes were normal (46,XY). Magnetic resonance imaging showed a hypoplastic pituitary gland.

Family History

The elder brother of patients 1 and 2 seemed healthy and unaffected. The father was examined and seemed unaffected. The mother suffered from epilepsy but was otherwise normal.

DISCUSSION

EEC syndrome (ectrodactyly, ectodermal dysplasia, and cleft lip and palate) is a rare autosomal-dominant disorder notable for its reduced penetrance and variable expressivity [Annerén et al., 1991; Bronstein and Gershoni-Baruch, 1993; Chranowska et al., 1990; Küster et al., 1985; Majewski and Küster, 1988; Penchaszadeh and de Negrotti, 1976; Predine-Hug et al., 1984; Preus and Fraser, 1973; Rodini and Richieri-Costa, 1990; Schmidt and Nitowsky, 1977; Tse et al., 1990; Walker and Clodius, 1963].

Ectodermal dysplasia is manifested by anomalies of hair, teeth, skin, and nails. These include complete or partial anodontia, microdontia, enamel hypoplasia, increased caries; sparse, fine, blond hair; dry and dystrophic skin; and thin, brittle nails. Anomalies of tear ducts and absence of the lacrimal puncta cause chronic inflammation of the eyes that may lead to corneal damage and blindness [Fried, 1972; Kaiser-Kupfer, 1973].

We report on 2 brothers with apparent EEC, hypogonadotropic hypogonadism, and a small pituitary gland on MRI. The exaggerated response to the TRH test in patient 2 could have resulted from either a primary thyroid disorder due to "mantle" irradiation for Hodgkin disease, or to tertiary hypothyroidism. Patient 1 demonstrated pituitary GH, TSH, and prolactin insufficiency.

The clinical manifestations seem to be quite similar in the 2 brothers reported here. They both have normal hair, no eye problems, dental anomalies, and pituitary insufficiency. One brother has a repaired cleft lip and lacks a toe, and the other brother has a repaired cleft lip and palate, syndactyly of fingers, and polysyndactyly of the left foot. The combination of limb anomalies, cleft lip and palate, and tooth anomalies is most compatible with the diagnosis of EEC syndrome, which is notable for its variable expressivity. Since our 2 patients do not fall within the classical definition of EEC syndrome, the possibility that they have a disorder similar to, yet different from, EEC has been considered. However, we are not aware of any other diagnosis that better fits our cases. Polysyndactyly, although rare, has been reported in EEC syndrome and should be regarded as one of its components [Annerén et al., 1991].

Hypogonadotropic hypogonadism was described previously in a boy with EEC syndrome [Van Maldergem et al., 1992]. Knudtzon and Aarskog [1987] reported on 2 patients with EEC and isolated growth-hormone deficiency. Both hypothalamic and pituitary developmental defects have been reported in patients with isolated cleft lip and palate [Ben-Amitai et al., 1990; Roitman and Laron, 1978].

On the basis of the 2 cases reported here, and the 3 sporadic cases reported previously [Knudtzon and Aarskog, 1987; Van Maldergem et al., 1992], we suggest that hypothalamopituitary insufficiency be included among the various manifestations of EEC syndrome. This manifestation, the prevalence of which remains to be ascertained, may have evaded attention and was thus underreported.

Gene carriers of EEC syndrome may manifest minimal abormalities; thus, we consider one of the two parents of our patients to be an asymptomatic gene carrier. Alternatively, this could be a (new) autosomal or X-linked recessive disorder.

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